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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/486,167 | 08/15/00 | KNOOPS B | VANM143.001A |

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| HUYNH, P | |
| ART UNIT | PAPER NUMBER |
| 1644 | 13 |

DATE MAILED: 11/06/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/486,167 | KNOOPS ET AL. | |
| | Examiner | Art Unit | |
| | " Neon" Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of* 37 CFR 1.136(a). *In no event, however, may a reply be timely filed* after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *8/15/00; 2/15/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5-9 and 12-27* is/are pending in the application.

4a) Of the above claim(s) *13,15 and 17-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9,12,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 5-9 and 12-27 are pending.

2. Applicant's election without traverse of Group II, claims 5-9, 12, 14 and 16 drawn to a nucleic acid, vector, host cell, pharmaceutical composition and diagnostic device comprising said nucleic acid, filed 2/15/01, is acknowledged.

3. Claims 13, 15 and 17-27 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 5-9, 12, 14 and 16 that read on nucleic acid are being acted upon in this Office Action.

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. The disclosure is objected to because of the following informalities: (1) SEQ ID NO: is required on page 18, line30; (2) the "n°" on page 20 lines 23-27 should have been "No.".

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5-9, 12, 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) two human polynucleotides consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encode a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, respectively, and polynucleotide probes of SEQ ID NOS: 7-9, and 11-16 (See page 7 of the specification) for in vitro diagnosis, does not reasonably provide enablement for (1) *any* polynucleotide encoding an amino acid sequence more than 70% homologous to SEQ ID NO: 2 and/or *any* polynucleotide comprising a polynucleotide more than 70% homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 5; (2) *any* polynucleotide more than 85%

homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 6; (3) *any* polynucleotide more than 95% homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 7; (4) *any* polynucleotide comprising SEQ ID NO: 1 or its complementary strand or a portion thereof specific for SEQ ID NO: 1 and comprising more than 15 base pairs as recited in claim 8; (5) *any* vector comprising said polynucleotide or its complementary strand; (6) *any* diagnostic device comprising said polynucleotide or its complementary strand or a portion thereof; (7) *any* pharmaceutical composition comprising a pharmaceutical acceptable carrier and any polynucleotide mentioned above or its complementary strand or a portion thereof and (8) *any* cell transformed by any vector comprising any polynucleotide mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only (1) a human polynucleotide (cDNA) consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 encoding a peroxisomal-associated polypeptides corresponding to SEQ ID NOS: 2, 4 and 6, from human, rat and mouse, respectively, (2) polynucleotide probes of SEQ ID NOS: 7-9 for in vitro diagnosis or monitoring lung injury associated with oxidative stress-related disorder.

The specification does not provide any guidance as how to make and use (1) *any* polynucleotide mentioned above for a pharmaceutical composition for treating *any* disease. There is insufficient guidance in the specification as filed as to which polynucleotide encoding an amino acid sequence more than 70% homologous to SEQ ID NO: 2. Furthermore, there is insufficient guidance in the specification as to which amino acid residue(s) within the full length amino acid sequence that after substitution, deletion or insertion will retain both the structure and function similar to SEQ ID NO: 2. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution,

addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that the nucleotide that encoding the amino acid sequence more than 70% homologous to SEQ ID NO: 2 is not enabled.

With regard to polynucleotide comprising a polynucleotide more than 70%, 85% or 95% homologous to SEQ ID NO: 1 or its complementary strand, it is known that the polynucleotide determines its protein coding properties. However, the predictability of which changes can be tolerated in a polynucleotide's nucleic acid sequence and still retain similar functions and properties requires a knowledge of, and guidance such as which nucleotide residues within the full-length polynucleotide are tolerant of modification and which nucleotide residues are conserved or less tolerant to modification in which the product's structure relates to its functional usefulness. Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Since the polynucleotide is only 70% homologous or similar to SEQ ID NO: 1, there is at least 30% differences. Furthermore, the transitional phrase "comprising" is open-ended and it expands the polynucleotide to include additional nucleotide at either end. Given the lack of guidance in the specification as filed as to which polynucleotide residues within the full-length polynucleotide of SEQ ID NO: 1 that after substitution, deletion or insertion will retain both the structure and function, it is unpredictable as to which polynucleotide "comprising" a polynucleotide more than 70% homologous to SEQ ID NO: 1 would have the same structure and function as SEQ ID NO: 1. Since the structure associated with functions of any polynucleotides more than 70% homologous to SEQ ID NO: 1 are undisclosed, it follows that its complementary strand is not enable. Likewise, the polynucleotide encoding more than 85% or 95% homologous to SEQ ID NO: 1 or its complementary strand as recited in claims 6 and 7 is also not enabled, along the lines of reasoning discussed supra.

With regard to "a portion thereof" as recited in claims 8, 12 and 14, the specification on page 6 defines that "a portion of SEQ ID NO: 1 is any nucleotide of more than 15 base pairs such as a primer, a probe or an antisense nucleotide". The state of the prior art as exemplified by Sambrook *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within oligonucleotide probes is unpredictable. Given that

the length of the polynucleotide is merely 15 base pairs, the claimed "a portion thereof" encompasses an infinite number of polynucleotide. Given the indefinite number of undisclosed polynucleotide, the insufficient guidance and working examples in the specification, the primer or probes that would hybridize specifically to any polynucleotide encoding an amino acid sequence more than 70% homologous to SEQ ID NO: 2 having similar function is unpredictable. Given the infinite number of undisclosed polynucleotide, the antisense polynucleotide that not only bind specifically to SEQ ID NO: 1 but also inhibit the expression of polypeptide at a cellular level would require undue experimentation of one skilled in the art to practice the claimed invention. Since the polynucleotide and portion thereof are not enable, it follows that the vector and host cell as recited in claims 9 and 16 comprising said polynucleotide are not enabled.

Claim 14 recites "a pharmaceutical composition" comprising a polynucleotide according to claim 5. However, the specification fails to provide any *in vivo* data, working examples, or guidance with respect to dosages as to treat a patient suffering from any disease using any of the polynucleotides mentioned above. A "pharmaceutical composition" comprises a "polynucleotide sequence encoding a peptide for treating any diseases in the absence of in vivo data is unpredictable for the following reasons: (1) efficacy of the polynucleotide has not been definitively demonstrated; (2) it is not always possible to extrapolate directly from in vitro experiments to in vivo studies; (3) the enhancing or maintaining high level expression of genes transferred to somatic cells may not persist or consistently achieved; (4) appropriate expression of polynucleotide transfer to specific cell types (target specificity) has not been demonstrated; (5) adverse reactions from the recipient may result; (6) the lower efficiency of gene transfer (naked nucleic acid) compared with viruses and the effective therapeutic amount have not been addressed.

Das *et al* teach that getting the antisense to the cell nuclei where their anti-gene action can take place can be difficult (See abstract, in particular).

Verma *et al* teach that the problem of gene therapy is the inability to deliver genes efficiently to the right type of cell, obtaining sustained expression of the therapeutic protein and without triggering the host immune responses (See page 239, in particular). Therefore, in the absence of in vivo working examples, it would require undue experimentation of one skilled in the art to practice the claimed invention.

*In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

9. Claims 5-9, 12, 14 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) *any* polynucleotide encoding an amino acid sequence more than 70% homologous to SEQ ID NO: 2 and/or *any* polynucleotide comprising a polynucleotide more than 70% homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 5; (2) *any* polynucleotide more than 85% homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 6; (3) *any* polynucleotide more than 95% homologous to SEQ ID NO: 1 or its complementary strand as recited in claim 7; (4) *any* polynucleotide comprising SEQ ID NO: 1 or its complementary strand or a portion thereof specific for SEQ ID NO: 1 and comprising more than 15 base pairs as recited in claim 8; (5) *any* vector comprising said polynucleotide or its complementary strand; (6) *any* diagnostic device comprising said polynucleotide or its complementary strand or a portion thereof; (7) *any* pharmaceutical composition comprising a pharmaceutical acceptable carrier and any polynucleotide mentioned above or its complementary strand or a portion thereof and (8) *any* cell transformed by any vector comprising any polynucleotide mentioned above.

The specification as filed discloses only (1) two human polynucleotide consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encode a peroxisomal-associated polypeptides of SEQ ID NOS: 2, 4 and 6 and polynucleotide probes of SEQ ID NOS: 7-9, and 11-16 (See page 7 of the specification).

There is no description about the structure associated with function of *any* polynucleotide mentioned above for in vitro diagnosis or for in vivo treatment of any disease. Given the lack of a written description of *any* additional representative species of polynucleotide as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al (Accession No. W00593, April 1996, PTO 892) or Hillier et al (Accession No. N91311, April 1996, PTO 892), or Hillier et al (Accession No. W38597, May 1996, PTO 892), or Hillier et al (Accession No. N68467, March 1996, PTO 892), or Hillier et al (Accession No. N42215, Jan 1996, PTO 892), or Hillier et al (Accession No. H20154, July 1995, PTO 892).

Hillier et al teach a portion of an isolated or purified polynucleotide specific for SEQ ID NO: 1 of instant application and comprising more than 15 base pairs (See Accession No. W00593, Accession No. N91311, Accession No. W38597, Accession No. N68467, Accession No. N42215, or Accession No. H20154). Thus, the reference teachings anticipate the claimed invention.

12. Claims 5-9, 12, 14 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by the US Pat No. 6,197,543 (Filed Oct 1997, PTO 892).

The '543 patent teaches an isolated or purified polynucleotide (See reference SEQ ID NO: 2 of '543 patent, in particular) that is 99.1% identical to the claimed polynucleotide of SEQ ID NO: 1 and its complementary strand. The reference polynucleotide encodes an amino acid sequence 100% identical to the polypeptide of SEQ ID NO: 2 of instant application (See polynucleotides 193 to 990 of reference polynucleotide SEQ ID NO: 2 of the '543 patent, in particular). The transitional phrase "comprising" is open-ended and it opens up the polynucleotide to include additional nucleotide at either end. Therefore, the claim reads on the reference polynucleotide. The '543 patent teaches partial neucleotide sequence or primers

comprising more than 15 base pairs or a portion of the reference SEQ ID NO: 2 of the '543 patent (See column 15, lines 57-66 bridging column 16, lines 1-11, in particular). The '543 patent further teaches a vector and host cell transformed with the reference polynucleotide or a fragment thereof to express the polypeptide (see column 17, lines 53- 67 bridging column 18, lines 1-2, column 20, lines 64-67 bridging column 21, lines 1-8, column 41, Expression of VMP, in particular). The '543 patent also teaches a diagnostic device such as microarray comprising the reference polynucleotide or a portion thereof as a target to monitor the expression level of large number of genes simultaneously (See column 33, lines 17-51, in particular). The '543 patent further teaches a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the reference nucleotide sequence of SEQ ID NO: 2. Since the reference polynucleotide is 99.1% identical to SEQ ID NO: 1 of instant application, the reference polynucleotide anticipates the claimed 70%, 85% and 95% homologous to SEQ ID: NO: 1 or its complementary strand. Given that the reference polynucleotide encodes an amino acid sequence that is 100% identical to the polypeptide of SEQ ID NO: 2 of instant application, the reference polypeptide anticipates the claimed polynucleotide encoding an amino acid sequence more than 70% homologous to SEQ ID NO: 2 of instant application. Thus, the reference teachings anticipate the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 9 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillier et al (Accession No. W00593, April 1996, PTO 892) or Hillier et al (Accession No. N91311, April 1996, PTO 892), or Hillier et al (Accession No. W38597, May 1996, PTO 892), or Hillier et al (Accession No. N68467, March 1996, PTO 892), or Hillier et al (Accession No. N42215, Jan 1996, PTO 892), or Hillier et al (Accession No. H20154, July 1995, PTO 892) or Marra et al (Accession No. W71344, June 1996, PTO 892), each in view of Sambrook et al (*Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

The teachings of Hillier et al have been discussed supra.

The claimed invention in claim 9 differs from the references only by the recitation of a vector comprising the said polynucleotide.

The claimed invention in claim 16 differs from the references only by the recitation of a cell transformed by the vector comprising a partial polynucleotide of SEQ ID NO: 1 or a homologue thereof.

Marra *et al* teach a partial polynucleotide from the mouse which is a homolog of a partial polynucleotide of SEQ ID NO: 1 of instant application.

Sambrook *et al* teach cloning a cDNA into an expression vector, and a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture. Sambrook *et al* teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce a peptide of interest using a portion of polynucleotide that is specific for SEQ ID NO: 1 of instant application as taught by Hillier et al or a portion of a polynucleotide from a homolog such as a mouse as taught by Marra et al by constructing an expression vector using the reference polynucleotide portion thereof to produce a recombinant host cell using the said expression vector and culturing the host cell under conditions which express the polypeptide in order to recover the polypeptide from the culture as taught by the Sambrook et al.

One having ordinary skill in the art at the time the invention was made would have been motivated to produce the polypeptide using recombinant techniques because there would be a higher yield of polypeptide with greater purity as taught by Sambrook *et al.*

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

18. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
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November 5, 2001

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